

Claims

1. A method of making a substituted pyrazolopyrimidine, the method comprising reacting an aminopyrazole compound or a salt thereof with a substituted 1-oxo-2-propenyl-compound or a salt thereof under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid.
2. The method of claim 1 wherein the reaction mixture further includes at least one phase-transfer agent.
3. The method of claim 2 wherein the at least one phase-transfer agent includes a water-soluble salt.
4. The method of claim 3 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.
5. The method of claim 1 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures, thereof.
6. The method of claim 5 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.
7. The method of claim 1 wherein the aqueous phase includes water.
8. The method of claim 1 wherein the aqueous phase includes at least one water miscible solvent or polymer selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropandiol, methanol, ethanol,

propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol, polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof.

9. The method of claim 1 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane, methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

10. The method of claim 1 further including extracting the pyrazolopyrimidine from the water immiscible organic liquid.

11. The method of claim 10 further included recrystallizing the extracted pyrazolopyrimidine.

12. The method of claim 1 wherein the pyrazolopyrimidine is zaleplon.

13. The method of claim 1 wherein the pyrazolopyrimidine is Indiplon™.

14. The method of claim 1 wherein the pyrazolopyrimidine is selected from the group consisting of:

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylpropanamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-propylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(polyethyleneglycol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(methoxyethyl)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(hydroxyethyl)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1',2'-propanediol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1'-propanol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(2'-propanol)acetamide;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

7-[3-[(methoxycarbonyl)methylamino]phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ether;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester;

ethyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, ethyl ester;

[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylacetamide;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

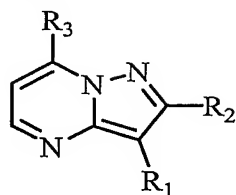
2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;
7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
6-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
3-bromo-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;
3-chloro-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;
7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine, pyridine-1-oxide;
2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
2,6-dimethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;
N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclobutanecarboxamide;
N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclopropanecarboxamide;
[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;
N-methyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-cyclopropanecarboxamide;
[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;
[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;
N-2-propenyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-acetamide;
ethyl[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]carbamic acid, ethyl ester;

N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;
N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;
N-methyl-N-(3-{3-[2-thienylcarbonyl]pyrazolo[1,5-a]pyrimidin-7-yl}phenyl)-
acetamide;

7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
ethyl 7 (α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
methyl 7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidin-3-yl ketone;
7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxaldehyde oxime;
7-(m-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
3-(methoxymethyl)-7-(α,α,α -trifluoro-m-tolyl)pyrazolo-[1,5-a]pyrimidine;
3-bromo-7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;
2-cyano-7(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
3-cyano-7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]-pyrimidine-2-acetonitrile;
3-methyl-7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;
ethyl 7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
ethyl 7-(3,4-xylyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
ethyl 7-(p-ethylphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
ethyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
7-(m-Fluorophenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
5-Phenylpyrazolo[1,5-a]pyrimidine; and
5-(α,α,α -Trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine.

15. A method of making a substituted pyrazolopyrimidine, or
pharmaceutically acceptable salt thereof, of Formula I,

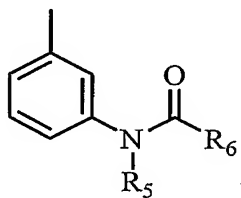


Formula I

wherein R_1 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, formyl, carboxyl, cyano, hydroxymethyl, N-hydroxyformimidoyl and R_4CO- wherein R_4 is selected from the group consisting of hydrogen; alkyl(C_1-C_6); alkoxy(C_1-C_6); unsubstituted phenyl; phenyl mono- or disubstituted by halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); phenyl (C_1-C_3), phenyl substituted by trifluoromethyl, alkylthio(C_1-C_3), alkylamino(C_1-C_3), dialkylamino(C_1-C_3), methylenedioxy, alkylsulfonyl(C_1-C_3) or alkanoylamino(C_1-C_3); naphthalenyl; thiazolyl; biphenyl; thienyl; furanyl; pyridinyl; substituted thiazolyl; substituted biphenyl; substituted thienyl; and substituted pyridinyl, wherein the substituents are selected from one or two of the groups consisting of halogen, alkyl(C_1-C_3) and alkoxy(C_1-C_3);

R_2 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, cyano, cyanomethyl, carbamoyl or alkyl (C_1-C_3); and

wherein R_3 is selected from the group consisting of phenyl; o-trifluoromethylphenyl; m-trifluoromethylphenyl; m-methoxyphenyl; pyridyl; pyridyl N-oxide; thienyl; furanyl; and substituted phenyl, wherein one or more of the positions is substituted by a group represented by Formula II



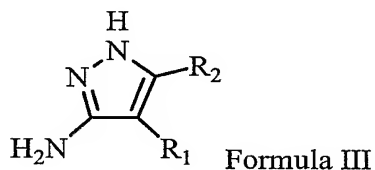
Formula II

wherein R_5 is selected from the group consisting of hydrogen, alkyl(C_1 - C_6), alkenyl(C_2 - C_6), alkynyl, cycloalkyl(C_3 - C_6)methyl, $-CH_2OCH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OH$, $-CH_2CHOHCH_2OH$, and $-[CH_2CH_2O]_{n=10-120}$; and

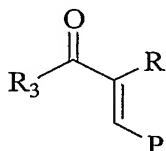
R_6 is selected from the group consisting of alkyl(C_1 - C_6), cycloalkyl(C_3 - C_6), $-O$ -alkyl(C_1 - C_6), $-NH$ -alkyl(C_1 - C_3), $-N$ -dialkyl(C_1 - C_3), $-(CH_2)_nO$ -alkyl(C_1 - C_3), $-(CH_2)_nNH$ -alkyl(C_1 - C_3) and $-(CH_2)_nN$ -dialkyl(C_1 - C_3), where n is an integer 1 to 3 inclusive;

the method comprising:

reacting a compound of Formula III or a salt thereof with a compound of Formula IV or a salt thereof under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid, wherein Formula III is



and Formula IV is



Formula IV

P is selected from the group consisting of $-Oac$, $-OR$, $-SR$ and $-NR'R$; and

R and R' are selected from the group consisting of hydrogen, alkyl(C_1 - C_6) and cyclic alkyl.

16. The method of claim 15 wherein the reaction mixture further includes at least one phase transfer agent.

17. The method of claim 16 wherein the at least one phase transfer agent includes but are not limited to the following: Aliquat® 336, ALKANOL®s, Polyethylene(PEG) esters and diesters, polypropylene glycol (PPG) and PEG-PPG copolymers, tetraalkylammonium salts, tetraalkylphosphonium salts, N-alkylpyridinium salts, sodium stearate, sodium palmitate, sodium laurate.

18. The method of claim 17 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

19. The method of claim 15 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures thereof.

20. The method of claim 19 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

21. The method of claim 15 wherein the aqueous phase includes water.

22. The method of claim 15 wherein the aqueous phase includes at least one water miscible solvent or polymer selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropanediol, methanol, ethanol, propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol,

polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof.

23. The method of claim 15 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane, methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

24. The method of claim 15 further including extracting the compound of Formula I from the water immiscible organic liquid.

25. The method of claim 24 further including recrystallizing the extracted compound of Formula I.

26. The method of claim 15 wherein Formula IV is N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide, Formula III is 3-amino-4-cyanopyrazole and Formula I is zaleplon.

27. The method of claim 15 wherein Formula IV is N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methylacetamide, Formula III is (3-amino-1H-pyrazol-4-yl)-2-thienylmethanone and Formula I is Indiplon™.

28. The method of claim 15 wherein Formula I is selected from the group consisting of N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(hydroxyethyl)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1',2'-propanediol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(1'-propanol)acetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-(2'-propanol)acetamide;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;

7-[3-((methoxycarbonyl)methylamino)phenyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid, ethyl ester;

[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, methyl ester;

ethyl(3-pyrazolo[1,5-a]pyrimidin-7-ylphenyl)carbamic acid, ethyl ester;

[3-(3-chloropyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;

N-[3-(3-cyanopyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylacetamide;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

2-ethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(3-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

6-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;

3-bromo-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;

3-chloro-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine;
7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine, pyridine-1-oxide;
2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
2,6-dimethyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
2-methyl-7-(3-pyridyl)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;
N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclobutanecarboxamide;
N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-methylcyclopropanecarboxamide;
[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;
N-methyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-cyclopropanecarboxamide;
[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]methylcarbamic acid, methyl ester;
[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]ethylcarbamic acid, ethyl ester;
N-2-propenyl-N-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]acetamide;
ethyl[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]carbamic acid, ethyl ester;
N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propenylacetamide;
N-[3-(3-benzoylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-2-propynylacetamide;
N-methyl-N-(3-{3-[2-thienylcarbonyl]pyrazolo[1,5-a]pyrimidin-7-yl}phenyl)acetamide;

7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
ethyl 7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
methyl 7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidin-3-yl ketone;
7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxaldehyde oxime;
7-(m-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
3-(methoxymethyl)-7-(α,α,α -trifluoro-m-tolyl)pyrazolo-[1,5-a]pyrimidine;
3-bromo-7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;
2-cyano-7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
3-cyano-7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]-pyrimidine-2-acetonitrile;
3-methyl-7-(α,α,α -trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine;
ethyl 7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
ethyl 7-(3,4-xylyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
ethyl 7-(p-ethylphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
ethyl 7-(3,4-dimethoxyphenyl)pyrazolo[1,5-a]pyrimidine-3-carboxylate;
7-(m-Fluorophenyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile;
5-Phenylpyrazolo[1,5-a]pyrimidine; and
5-(α,α,α -Trifluoro-m-tolyl)pyrazolo[1,5-a]pyrimidine.

29. A method for making zaleplon, the method comprising:

reacting N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethylacetamide with 3-amino-4-cyanopyrazole under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid.

30. The method of claim 29 wherein the reaction mixture further includes at least one phase transfer agent.

31. The method of claim 30 wherein the at least one phase transfer agent includes a water soluble salt.

32. The method of claim 31 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

33. The method of claim 29 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures thereof.

34. The method of claim 33 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

35. The method of claim 29 wherein the aqueous phase includes water.

36. The method of claim 29 wherein the aqueous phase includes at least one water miscible solvent or polymer selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropanediol, methanol, ethanol, propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol, polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof.

37. The method of claim 29 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane,

methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

38. The method of claim 29 further including extracting the zaleplon from the water immiscible organic liquid.

39. The method of claim 38 further included recrystallizing the extracted zaleplon.

40. A method for making Indiplon™, the method comprising:
reacting N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methylacetamide with (3-amino-1H-pyrazol-4-yl)-2-thienylmethanone under acidic conditions in a reaction medium including a two-phase mixture of an aqueous solution and a water-immiscible organic liquid.

41. The method of claim 40 wherein the reaction mixture further includes at least one phase transfer agent.

42. The method of claim 41 wherein the at least one phase transfer agent includes a water soluble salt.

43. The method of claim 42 wherein the water soluble salt includes a salt selected from the group consisting of sodium chloride, sodium bromide, sodium sulfate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium phosphate, sodium acetate, ammonium acetate, sodium tartrate, sodium benzoate, sodium phthalate and mixtures thereof.

44. The method of claim 40 wherein the acidic conditions are prepared by the addition of at least one acid including an acid selected from the group consisting of at least one mineral acid, at least one organic acid and mixtures thereof.

45. The method of claim 44 wherein the at least one acid includes at least one acid selected from the group consisting of hydrochloric, hydrobromic, hydrofluoric, sulfuric, acetic, formic, methanesulfonic, p-toluenesulfonic, trifluoroacetic, hexanesulfonic, heptafluorobutyric, perchloric, nitric, phosphoric acid and mixtures thereof.

46. The method of claim 40 wherein the aqueous phase includes water.

47. The method of claim 40 wherein the aqueous phase includes at least one water miscible solvent selected from the group consisting of formamide, acetamide, 1-methyl-2-pyrrolidinone, DMF, DMAC, DMSO, hexamethylphosphoramide, hexamethylphosphortriamide, methylsulfone, sulfolane, 1-methylpropanediol, methanol, ethanol, propanol, butanol, acetonitrile, propionitrile, THF, glycol ethers, acetone, dioxane, nitromethane, nitroethane, polyethylene glycol, polyoxyethylene, polyglycerol, polyvinylpyrrolidone, polyvinyl alcohol and mixtures thereof..

48. The method of claim 40 wherein the water immiscible organic liquid includes an organic liquid selected from the group consisting of chloroform, dichloromethane, hexane and hexane compounds, heptane, cyclohexane, methylcyclohexane, anisole, fluorobenzene, chlorobenzene, toluene, xylene and xylene compounds, diethylether, tert-butylmethylether, n-propyl formate, ethyl acetate, butyl acetate, propyl acetate, isoamyl acetate, 2-butanone, 2-hexanone, 3-methyl-2-pentanone, 4-methyl-2-pentanone, pinacolone, 2-heptanone, acetophenone, cyclohexanone, cyclopentanone, long-chained alcohols, for example; decanol, dodecanol and mixtures thereof.

49. The method of claim 40 further including extracting Indiplon™ from the water immiscible organic liquid.

50. The method of claim 40 further included recrystallizing the extracted Indiplon™.